

Notice of Allowability	Application No.	Applicant(s)	
	09/917,789	LYNCH ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 27 August 2003.
2. ☒ The allowed claim(s) is/are 95-101, 103-114, 116-127, 129-140, 142-153, 155-166, 168-179, 181-192, 194-205, 207-219, 221-232, 234-245, 247-258, 260-271, 273-284, 286-297, 299-310, 312-323 and 325-330.
3. ☒ The drawings filed on 27 August 2003 are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
- * Certified copies not received: _____.
5. ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
8. ☐ CORRECTED DRAWINGS must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No. _____.
 - (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
 - (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1 <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 2 <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3 <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 4 <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No. _____ |
| 5 <input checked="" type="checkbox"/> Information Disclosure Statements (PTO-1449), Paper No. _____ | 6 <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 7 <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material | 8 <input type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9 <input type="checkbox"/> Other _____ |

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 27 August 2003 has been received and entered in full. Claims 1-94 have been cancelled and claims 95-330 have been added.

Withdrawn Objections And/Or Rejections

2. The Objection to the Specification as set forth at pp. 2-3 ¶4-7 in the previous Office Action (27 February 2003) is *withdrawn* in view of Applicant's amendments (Amendment and Reply, 27 August 2003).

3. The rejection of claims 1-12 under 35 U.S.C. §112 ¶1 as set forth at pp. 3-7 ¶8-16 in the previous Office Action (27 February 2003) is *withdrawn* in view of Applicant's amendments (Amendment and Reply, 27 August 2003).

4. The rejection of claims 1-12 under 35 U.S.C. §112 ¶2 as set forth at pp. 7 ¶17 in the previous Office Action (27 February 2003) is *withdrawn* in view of Applicant's amendments (Amendment and Reply, 27 August 2003).

5. The Declaration of Xiaoning Bi and Gary Lynch filed on 27 August 2003 under 37 CFR 1.131 is sufficient to overcome the Bi *et al.* (21 March 2000) "Novel Cathepsin D Inhibitors Block the Formation of Hyperphosphorylated Tau Fragments in Hippocampus." Journal of Neurochemistry 74(4): 1469-1477 reference. Thus the rejection of claims 1-9 under 35 U.S.C. §102(a) as set forth at pp. 8 ¶18-20 in the previous Office Action (27 February 2003) is *moot*.

EXAMINER'S AMENDMENT

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6. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Claim ~~95~~¹ (Currently Amended) An in vitro method of determining the effect of a substance on characteristics that are indicative of Alzheimer's Disease ~~or related neurodegenerative disorders~~ in rodent brain cells, said method comprising:

- (A) exposing said brain cells to a cathepsin D-increasing agent or compound under conditions that increase the concentration or amount of cathepsin D in said cells to an effective concentration,
- (B) maintaining said cells for a time that is sufficient to induce, relative to the levels present in the absence of said substance, one or more characteristics indicative of ~~said~~ Alzheimer's Disease ~~or said related neurodegenerative disorders~~ in said cells as a result of said increase in said cathepsin D,
- (C) adding said substance before, during and/or after said exposing or said maintaining; and
- (D) determining whether the presence of said substance has an effect on the induction of said one or more characteristics, wherein said characteristics are selected from the group consisting of:
 - (1) the formation of neurofibrillary tangles,
 - (2) the hyperphosphorylation of tau,
 - (3) the fragmentation of tau,
 - (4) the production and/or release of brain-produced cytokines TGF-beta, IL-1b, or TNF, ~~or~~ LPS,

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(5) a microglia reaction or microglial activation,
(6) indications of brain inflammatory reactions,
(7) conversion of p35 to p25,
(8) changes in the level and/or activity of cyclin dependent protein kinase 5 (cdk5), and
(9) changes in the level and/or activity of mitogen activated protein kinases (MAPK), wherein
said effect on said induction of any or all of said characteristics in D(1)- D(9) is indicative of the
appearance or disappearance, respectively, of said characteristics of said Alzheimer's Disease or
~~said related neurodegenerative disorders, wherein said related neurodegenerative disorder is one~~
~~in which exposing said rodent brain cells to a cathepsin D-increasing agent or compound under~~
~~conditions that increase the concentration or amount of cathepsin D in said cells to an effective~~
~~concentration induces one or more of said characteristics of D(1)-D(9).~~

²
Claim ~~96~~ (Previously Added): The method of claim ~~95~~¹, wherein said characteristic is said
formation of neurofibrillary tangles.

³
Claim ~~97~~ (Currently Amended) The method of claim ~~95~~¹, wherein said compound is selected
from the group consisting of ~~a compound which is selected from the group consisting of~~
chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-
phenylalanine-diazomethylketone, and beta-amyloid.

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⁴
Claim ~~98~~ (Currently Amended) The method of claim ~~97~~³, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

⁵
Claim ~~99~~ (Previously Added): The method of claim ~~96~~², wherein said brain cells are in the form of dissociated cells.

⁶
Claim ~~100~~ (Previously Added): The method of claim ~~96~~², wherein said brain cells are in the form of a brain slice.

⁷
Claim ~~101~~ (Currently Amended) The method of claim ~~100~~⁶, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 102 (Cancelled)

⁸
Claim ~~103~~ (Currently Amended) The method of any one of claims ~~96-102~~²⁻⁷ ~~96-101~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

⁹
Claim ~~104~~ (Previously Added) The method of claim ~~103~~⁸, wherein said rodent is a mouse.

¹⁰
Claim ~~105~~ (Previously Added) The method of claim ~~103~~⁸, wherein said rodent is a rat.

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¹¹
Claim ~~106~~²⁻⁷ (Currently Amended) The method of any one of claims 96-102 ~~96-101~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹²
Claim ~~107~~¹¹ (Previously Added) The method of claim ~~106~~, wherein said rodent is a mouse.

¹³
Claim ~~108~~¹¹ (Previously Added) The method of claim ~~106~~, wherein said rodent is a rat.

¹⁴
Claim ~~109~~¹ (Previously Added) The method of claim ~~95~~, wherein said characteristic is said hyperphosphorylation of tau.

¹⁵
Claim ~~110~~¹⁴ (Currently Amended) The method of claim ~~109~~, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹⁶
Claim ~~111~~¹⁵ (Currently Amended) The method of claim ~~110~~, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹⁷
Claim ~~112~~¹⁴ (Previously Added) The method of claim ~~109~~, where said brain cells are in the form of dissociated cells.

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¹⁸
Claim ~~113~~ (Previously Added): The method of claim ~~109~~¹⁴, wherein said brain cells are in the form of a brain slice.

¹⁹
Claim ~~114~~ (Currently Amended) The method of claim ~~113~~¹⁸, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 115 (Cancelled)

²⁰
Claim ~~116~~ (Currently Amended) The method of any one of claims ~~109-115~~¹⁴⁻¹⁹ ~~109-114~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

²¹
Claim ~~117~~ (Previously Added) The method of claim ~~116~~²⁰, wherein said rodent is a mouse.

²²
Claim ~~118~~ (Previously Added) The method of claim ~~116~~²⁰, wherein said rodent is a rat.

²³
Claim ~~119~~ (Currently Amended) The method of any one of claims ~~109-115~~¹⁴⁻¹⁹ ~~109-114~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

²⁴
Claim ~~120~~ (Previously Added) The method of claim ~~119~~²³, wherein said rodent is a mouse.

²⁵
Claim ~~121~~ (Previously Added) The method of claim ~~119~~²³, wherein said rodent is a rat.

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²⁶
Claim ~~122~~ (Previously Added) The method of claim ~~95~~¹, wherein said characteristic is said fragmentation of tau.

²⁷
Claim ~~123~~ (Currently Amended) The method of claim ~~122~~²⁶, wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

²⁸
Claim ~~124~~ (Currently Amended) The method of claim ~~123~~²⁷, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

²⁹
Claim ~~125~~ (Previously Added) The method of claim ~~122~~²⁶, where said brain cells are in the form of dissociated cells.

³⁰
Claim ~~126~~ (Previously Added): The method of claim ~~122~~²⁶, wherein said brain cells are in the form of a brain slice.

³¹
Claim ~~127~~ (Currently Amended) The method of claim ~~126~~³⁰, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

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Claim 128 (Cancelled)

³²
Claim ~~129~~ (Currently Amended) The method of any one of claims ~~122-128~~ ²⁶⁻³¹ ~~122-127~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

³³
Claim ~~130~~ (Previously Added) The method of claim ~~129~~ ³², wherein said rodent is a mouse.

³⁴
Claim ~~131~~ (Previously Added) The method of claim ~~129~~ ³², wherein said rodent is a rat.

³⁵
Claim ~~132~~ (Currently Amended) The method of any one of claims ~~122-128~~ ²⁶⁻³¹ ~~122-127~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

³⁶
Claim ~~133~~ (Previously Added) The method of claim ~~132~~ ³⁵, wherein said rodent is a mouse.

³⁷
Claim ~~134~~ (Previously Added) The method of claim ~~132~~ ³⁵, wherein said rodent is a rat.

³⁸
Claim ~~135~~ (Currently Amended) The method of claim ~~95~~ ¹, wherein said characteristic is said production and/or release of brain-produced cytokines TGF-beta, IL-1b, or TNF ~~or LPS~~.

³⁹
Claim ~~136~~ (Currently Amended) The method of claim ~~135~~ ³⁸, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of

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chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

⁴⁰
Claim ~~137~~ (Currently Amended) The method of claim ~~136~~³⁹, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

⁴¹
Claim ~~138~~ (Previously Added) The method of claim ~~135~~³⁸, where said brain cells are in the form of dissociated cells.

⁴²
Claim ~~139~~ (Previously Added): The method of claim ~~135~~³⁸, wherein said brain cells are in the form of a brain slice.

⁴³
Claim ~~140~~ (Currently Amended) The method of claim ~~139~~⁴², wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 141 (Cancelled)

⁴⁴
Claim ~~142~~ (Currently Amended) The method of any one of claims ~~135-141~~³⁸⁻⁴³ ~~135-140~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

⁴⁵
Claim ~~143~~ (Previously Added) The method of claim ~~142~~⁴⁴, wherein said rodent is a mouse.

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⁴⁶
Claim ~~144~~ (Previously Added) The method of claim ⁴⁵~~143~~, wherein said rodent is a rat.

⁴⁷
Claim ~~145~~ (Currently Amended) The method of any one of claims ~~135-141~~ ³⁸⁻⁴³ ~~135-140~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

⁴⁸
Claim ~~146~~ (Previously Added) The method of claim ⁴⁷~~145~~, wherein said rodent is a mouse.

⁴⁹
Claim ~~147~~ (Previously Added) The method of claim ⁴⁷~~145~~, wherein said rodent is a rat.

⁵⁰
Claim ~~148~~ (Previously Added) The method of claim ¹~~95~~, wherein said characteristic is said microglia reaction or microglial activation.

⁵¹
Claim ~~149~~ (Currently Amended) The method of claim ⁵⁰~~148~~, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

⁵²
Claim ~~150~~ (Currently Amended) The method of claim ⁵¹~~149~~, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

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⁵³
Claim ~~151~~ (Previously Added) The method of claim ~~148~~⁵⁰, where said brain cells are in the form of dissociated cells.

⁵⁴
Claim ~~152~~ (Previously Added): The method of claim ~~148~~⁵⁰, wherein said brain cells are in the form of a brain slice.

⁵⁵
Claim ~~153~~ (Currently Amended) The method of claim ~~152~~⁵⁴, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 154 (Cancelled)

⁵⁶
Claim ~~155~~ (Currently Amended) The method of any one of claims ~~148-154~~⁵⁰⁻⁵⁵ ~~148-155~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

⁵⁷
Claim ~~156~~ (Previously Added) The method of claim ~~155~~⁵⁶, wherein said rodent is a mouse.

⁵⁸
Claim ~~157~~ (Previously Added) The method of claim ~~155~~⁵⁶, wherein said rodent is a rat.

⁵⁹
Claim ~~158~~ (Currently Amended) The method of any one of claims ~~148-154~~⁵⁰⁻⁵⁵ ~~148-155~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

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⁶⁰
Claim ~~159~~ (Previously Added) The method of claim ~~158~~⁵⁹, wherein said rodent is a mouse.

⁶¹
Claim ~~160~~ (Previously Added) The method of claim ~~158~~⁵⁹, wherein said rodent is a rat.

⁶²
Claim ~~161~~ (Previously Added) The method of claim ~~98~~¹, wherein said characteristic is said indications of brain inflammatory reactions.

⁶³
Claim ~~162~~ (Currently Amended) The method of claim ~~161~~⁶², wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

⁶⁴
Claim ~~163~~ (Currently Amended) The method of claim ~~162~~⁶³, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

⁶⁵
Claim ~~164~~ (Previously Added) The method of claim ~~163~~⁶⁴, where said brain cells are in the form of dissociated cells.

⁶⁶
Claim ~~165~~ (Previously Added): The method of claim ~~164~~⁶², wherein said brain cells are in the form of a brain slice.

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⁶⁷
Claim ~~166~~ (Currently Amended) The method of claim ~~165~~⁶⁶, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, or and a cortex slice.

Claim 167 (Cancelled)

⁶⁸
Claim ~~168~~ (Currently Amended) The method of any one of claims ~~161-167~~⁶²⁻⁶⁷ ~~161-166~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

⁶⁹
Claim ~~169~~ (Previously Added) The method of claim ~~168~~⁶⁸, wherein said rodent is a mouse.

⁷⁰
Claim ~~170~~ (Previously Added) The method of claim ~~168~~⁶⁸, wherein said rodent is a rat.

⁷¹
Claim ~~171~~ (Currently Amended) The method of any one of claims ~~161-167~~⁶²⁻⁶⁷ ~~161-166~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

⁷²
Claim ~~172~~ (Previously Added) The method of claim ~~171~~⁷¹, wherein said rodent is a mouse.

⁷³
Claim ~~173~~ (Previously Added) The method of claim ~~171~~⁷¹, wherein said rodent is a rat.

⁷⁴
Claim ~~174~~ (Previously Added) The method of claim ~~95~~¹, wherein said characteristic is said conversion of p35 to p25.

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⁷⁵
Claim ~~173~~ (Currently Amended) The method of claim ~~174~~⁷⁴, wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

⁷⁶
Claim ~~176~~ (Currently Amended) The method of claim ~~174~~⁷⁵ ~~175~~, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

⁷⁷
Claim ~~177~~ (Previously Added) The method of claim ~~174~~⁷⁴, where said brain cells are in the form of dissociated cells.

⁷⁸
Claim ~~178~~ (Previously Added): The method of claim ~~174~~⁷⁴, wherein said brain cells are in the form of a brain slice.

⁷⁹
Claim ~~179~~ (Currently Amended) The method of claim ~~178~~⁷⁸, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 180 (Cancelled)

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⁸⁰
Claim ~~181~~ (Currently Amended) The method of any one of claims ~~174-180~~ ⁷⁴⁻⁷⁹ ~~174-179~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

⁸¹
Claim ~~182~~ (Previously Added) The method of claim ~~181~~ ⁸⁰, wherein said rodent is a mouse.

⁸²
Claim ~~183~~ (Previously Added) The method of claim ~~181~~ ⁸⁰, wherein said rodent is a rat.

⁸³
Claim ~~184~~ (Currently Amended) The method of any one of claims ~~174-180~~ ⁷⁴⁻⁷⁹ ~~174-179~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

⁸⁴
Claim ~~185~~ (Previously Added) The method of claim ~~184~~ ⁸³, wherein said rodent is a mouse.

⁸⁵
Claim ~~186~~ (Previously Added) The method of claim ~~185~~ ⁸⁴, wherein said rodent is a rat.

⁸⁶
Claim ~~187~~ (Previously Added) The method of claim ~~95~~ ¹, wherein said characteristic is said changes in the level and/or activity of cyclin dependent protein kinase 5 (cdk5).

⁸⁷
Claim ~~188~~ (Currently Amended) The method of claim ~~187~~ ⁸⁶, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

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⁸⁸
Claim ~~189~~ (Currently Amended) The method of claim ⁸⁷~~188~~, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

⁸⁹
Claim ~~190~~ (Previously Added) The method of claim ⁸⁶~~187~~, where said brain cells are in the form of dissociated cells.

⁹⁰
Claim ~~191~~ (Previously Added): The method of claim ⁸⁶~~187~~, wherein said brain cells are in the form of a brain slice.

⁹¹
Claim ~~192~~ (Currently Amended) The method of claim ⁹⁰~~191~~, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 193 (Cancelled)

⁹²
Claim ~~194~~ (Currently Amended) The method of any one of claims ~~187-193~~ ⁸⁶⁻⁹¹~~187-192~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

⁹³
Claim ~~195~~ (Previously Added) The method of claim ⁹²~~194~~, wherein said rodent is a mouse.

⁹⁴
Claim ~~196~~ (Previously Added) The method of claim ⁹²~~194~~, wherein said rodent is a rat.

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⁹⁵
Claim ~~197~~ (Currently Amended) The method of any one of claims ~~187-193~~ ⁸⁶⁻⁹¹ ~~187-192~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

⁹⁶
Claim ~~198~~ (Previously Added) The method of claim ~~197~~ ⁹⁵, wherein said rodent is a mouse.

⁹⁷
Claim ~~199~~ (Previously Added) The method of claim ~~197~~ ⁹⁵, wherein said rodent is a rat.

⁹⁸
Claim ~~200~~ (Previously Added) The method of claim ~~98~~ ¹, wherein said characteristic is said changes in the level and/or activity of mitogen activated protein kinases.

⁹⁹
Claim ~~201~~ (Currently Amended) The method of claim ~~200~~ ⁹⁸, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹⁰⁰
Claim ~~202~~ (Currently Amended) The method of claim ~~201~~ ⁹⁹, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹⁰¹
Claim ~~203~~ (Previously Added) The method of claim ~~200~~ ⁹⁸, where said brain cells are in the form of dissociated cells.

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¹⁰²
Claim ~~204~~ (Previously Added): The method of claim ~~200~~⁹⁸, wherein said brain cells are in the form of a brain slice.

¹⁰³
Claim ~~205~~ (Currently Amended) The method of claim ~~204~~¹⁰², wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 206 (Cancelled)

¹⁰⁴
Claim ~~207~~ (Currently Amended) The method of any one of claims 200-206 ~~200-205~~⁹⁸⁻¹⁰³, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹⁰⁵
Claim ~~208~~ (Previously Added) The method of claim ~~207~~¹⁰⁴, wherein said rodent is a mouse.

¹⁰⁶
Claim ~~209~~ (Previously Added) The method of claim ~~207~~¹⁰⁴, wherein said rodent is a rat.

¹⁰⁷
Claim ~~210~~ (Currently Amended) The method of any one of claims 200-206 ~~200-205~~⁹⁸⁻¹⁰³, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹⁰⁸
Claim ~~211~~ (Previously Added) The method of claim ~~210~~¹⁰⁷, wherein said rodent is a mouse.

¹⁰⁹
Claim ~~212~~ (Previously Added) The method of claim ~~210~~¹⁰⁷, wherein said rodent is a rat.

110
Claim ~~213~~ (Currently Amended) An in vitro method of determining the effect of a substance on characteristics that are indicative of Alzheimer's Disease ~~or related neurodegenerative disorders~~ in rodent brain cells, said method comprising:

(A) exposing said brain cells to a condition that disrupts lysosomal activity in said cells, wherein said condition comprises contacting said cells with a compound that disrupts lysosomal activity,

(B) maintaining said cells for a time that is sufficient to induce, relative to the levels present in the absence of said substance, one or more characteristics indicative of said Alzheimer's Disease ~~or said neurodegenerative disorders~~ in said cells as a result of said disruption of said lysosomal activity,

(C) adding said substance before, during and/or after said exposing or said maintaining; and

(D) determining whether the presence of said substance has an effect on the induction of said one or more characteristics, wherein said characteristics are selected from the group consisting of:

(1) the formation of neurofibrillary tangles,

(2) the hyperphosphorylation of tau,

(3) the fragmentation of tau,

(4) the production and/or release of brain-produced cytokines TGF-beta, IL-1b, or TNF, ~~or~~ LPS,

(5) a microglia reaction or microglial activation,

(6) indications of brain inflammatory reactions, conversion of p35 to p25,

(8) changes in the level and/or activity of cyclin dependent protein kinase 5 (cdk5), and

(9) changes in the level and/or activity of mitogen activated protein kinases (MAPK), wherein

said effect on said induction of any or all of said characteristics in D(1)- D(9) is indicative of the

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appearance or disappearance, respectively, of said characteristics of said Alzheimer's Disease or ~~said related neurodegenerative disorders, wherein said related neurodegenerative disorder is one in which exposing rodent brain cells to a condition that disrupts lysosomal activity in said cells, induces one or more of said characteristics of D(1)-D(9).~~

¹¹¹
Claim ~~214~~ (Previously Added) The method of claim ~~213~~¹¹⁰, wherein said characteristic is said formation of neurofibrillary tangles.

¹¹²
Claim ~~215~~ (Currently Amended) The method of claim ~~214~~¹¹¹, wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹¹³
Claim ~~216~~ (Currently Amended) The method of claim ~~215~~¹¹², wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹¹⁴
Claim ~~217~~ (Previously Added) The method of claim ~~214~~¹¹¹, where said brain cells are in the form of dissociated cells.

¹¹⁵
Claim ~~218~~ (Previously Added): The method of claim ~~214~~¹¹¹, wherein said brain cells are in the form of a brain slice.

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¹¹⁵
¹¹⁶ Claim ~~219~~ (Currently Amended) The method of claim ~~218~~, wherein said brain slice is selected
from the group consisting of a hippocampal slice, an entorhinal cortex slice, an
entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 220 (Cancelled)

¹¹⁷ Claim ~~221~~ (Currently Amended) The method of any one of claims 214-220 ~~214-219~~, wherein
¹¹¹⁻¹¹⁶ said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹¹⁸ Claim ~~222~~ (Previously Added) The method of claim ~~221~~, wherein said rodent is a mouse.
¹¹⁷

¹¹⁹ Claim ~~223~~ (Previously Added) The method of claim ~~222~~, wherein said rodent is a rat.
¹¹⁸

¹²⁰ Claim ~~224~~ (Currently Amended) The method of any one of claims 214-220 ~~214-219~~, wherein
¹¹¹⁻¹¹⁶ said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹²¹ Claim ~~225~~ (Previously Added) The method of claim ~~224~~, wherein said rodent is a mouse.
¹²⁰

¹²² Claim ~~226~~ (Previously Added) The method of claim ~~224~~, wherein said rodent is a rat.
¹²⁰

¹²³ Claim ~~227~~ (Previously Added) The method of claim ~~215~~, wherein said characteristic is
¹¹⁰ hyperphosphorylation of tau.

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¹²⁴
Claim ~~228~~ (Currently Amended) The method of claim ~~227~~¹²³, wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹²⁵
Claim ~~229~~ (Currently Amended) The method of claim ~~228~~¹²⁴, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹²⁶
Claim ~~230~~ (Previously Added) The method of claim ~~227~~¹²³, where said brain cells are in the form of dissociated cells.

¹²⁷
Claim ~~231~~ (Previously Added): The method of claim ~~227~~¹²³, wherein said brain cells are in the form of a brain slice.

¹²⁸
Claim ~~232~~ (Currently Amended) The method of claim ~~231~~¹²⁷, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 233 (Cancelled)

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¹²⁹
Claim ~~234~~ (Currently Amended) The method of any one of claims ~~227-233~~ ¹²³⁻¹²⁸ ~~227-232~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹³⁰
Claim ~~235~~ (Previously Added) The method of claim ~~234~~ ¹²⁹, wherein said rodent is a mouse.

¹³¹
Claim ~~236~~ (Previously Added) The method of claim ~~234~~ ¹²⁹, wherein said rodent is a rat.

¹³²
Claim ~~237~~ (Currently Amended) The method of any one of claims ~~227-233~~ ¹²³⁻¹²⁸ ~~227-232~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹³³
Claim ~~238~~ (Previously Added) The method of claim ~~237~~ ¹³², wherein said rodent is a mouse.

¹³⁴
Claim ~~239~~ (Previously Added) The method of claim ~~237~~ ¹³², wherein said rodent is a rat.

¹³⁵
Claim ~~240~~ (Previously Added) The method of claim ~~212~~ ¹¹⁰, wherein said characteristic is said fragmentation of tau.

¹³⁶
Claim ~~241~~ (Currently Amended) The method of claim ~~240~~ ¹³⁵, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

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¹³⁷
Claim ~~242~~ (Currently Amended) The method of claim ¹³⁶~~241~~, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹³⁸
Claim ~~243~~ (Previously Added) The method of claim ¹³⁵~~240~~, where said brain cells are in the form of dissociated cells.

¹³⁹
Claim ~~244~~ (Previously Added): The method of claim ¹³⁵~~240~~, wherein said brain cells are in the form of a brain slice.

¹⁴⁰
Claim ~~245~~ (Currently Amended) The method of claim ¹³⁹~~244~~, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 246 (Cancelled)

¹⁴¹
Claim ~~247~~ (Currently Amended) The method of any one of claims ~~240-246~~ ¹³⁵⁻¹⁴⁰~~240-245~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹⁴²
Claim ~~248~~ (Previously Added) The method of claim ¹⁴¹~~247~~, wherein said rodent is a mouse.

¹⁴³
Claim ~~249~~ (Previously Added) The method of claim ¹⁴¹~~247~~, wherein said rodent is a rat.

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¹⁴⁴
Claim ~~250~~ (Currently Amended) The method of any one of claims ~~240-246~~ ¹³⁵⁻¹⁴⁰ ~~240-245~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹⁴⁵
Claim ~~251~~ (Previously Added) The method of claim ~~250~~ ¹⁴⁴, wherein said rodent is a mouse.

¹⁴⁶
Claim ~~252~~ (Previously Added) The method of claim ~~250~~ ¹⁴⁴, wherein said rodent is a rat.

¹⁴⁷
Claim ~~253~~ (Currently Amended) The method of claim ~~213~~ ¹¹⁰, wherein said characteristic is said production and/or release of brain-produced cytokines TGF-beta, IL-1b, or TNF ~~or~~ LPS.

¹⁴⁸
Claim ~~254~~ (Currently Amended) The method of claim ~~240~~ ¹³⁵, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹⁴⁹
Claim ~~255~~ (Currently Amended) The method of claim ~~254~~ ¹⁴⁸, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹⁵⁰
Claim ~~256~~ (Previously Added) The method of claim ~~255~~ ¹⁴⁸, where said brain cells are in the form of dissociated cells.

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Claim ~~257~~¹⁵¹ (Previously Added): The method of claim ~~253~~¹⁴⁷, wherein said brain cells are in the form of a brain slice.

Claim ~~258~~¹⁵² (Currently Amended) The method of claim ~~257~~¹⁵¹, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 259 (Cancelled)

Claim ~~260~~¹⁵³ (Currently Amended) The method of any one of claims 253-259 ~~253-258~~¹⁴⁷⁻¹⁵², wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

Claim ~~261~~¹⁵⁴ (Previously Added) The method of claim ~~260~~¹⁵³, wherein said rodent is a mouse.

Claim ~~262~~¹⁵⁵ (Previously Added) The method of claim ~~260~~¹⁵³, wherein said rodent is a rat.

Claim ~~263~~¹⁵⁶ (Currently Amended) The method of any one of claims 253-259 ~~253-258~~¹⁴⁷⁻¹⁵², wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

Claim ~~264~~¹⁵⁷ (Previously Added) The method of claim ~~263~~¹⁵⁶, wherein said rodent is a mouse.

Claim ~~265~~¹⁵⁸ (Previously Added) The method of claim ~~263~~¹⁵⁶, wherein said rodent is a rat.

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Claim ~~266~~¹⁵⁹ (Previously Added) The method of claim ~~215~~¹¹⁰, wherein said characteristic is said microglia reaction or microglial activation.

Claim ~~267~~¹⁶⁰ (Currently Amended) The method of claim ~~266~~¹⁵⁹, wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

Claim ~~268~~¹⁶¹ (Currently Amended) The method of claim ~~267~~¹⁶⁰, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

Claim ~~269~~¹⁶² (Previously Added): The method of claim ~~266~~¹⁵⁹, wherein said brain cells are in the form of dissociated cells.

Claim ~~270~~¹⁶³ (Previously Added): The method of claim ~~266~~¹⁵⁹, wherein said brain cells are in the form of a brain slice.

Claim ~~271~~¹⁶⁴ (Currently Amended) The method of claim ~~270~~¹⁶³, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

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Claim 272 (Cancelled)

¹⁶⁵
Claim ~~273~~ (Currently Amended) The method of any one of claims ~~266-272~~ ¹⁵⁹⁻¹⁶⁴ ~~266-271~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹⁶⁶
Claim ~~274~~ (Previously Added) The method of claim ~~273~~ ¹⁶⁵, wherein said rodent is a mouse.

¹⁶⁷
Claim ~~275~~ (Previously Added) The method of claim ~~273~~ ¹⁶⁵, wherein said rodent is a rat.

¹⁶⁸
Claim ~~276~~ (Currently Amended) The method of any one of claims ~~266-272~~ ¹⁵⁹⁻¹⁶⁴ ~~266-271~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹⁶⁹
Claim ~~277~~ (Previously Added) The method of claim ~~276~~ ¹⁶⁸, wherein said rodent is a mouse.

¹⁷⁰
Claim ~~278~~ (Previously Added) The method of claim ~~276~~ ¹⁶⁸, wherein said rodent is a rat.

¹⁷¹
Claim ~~279~~ (Previously Added) The method of claim ~~278~~ ¹¹⁰, wherein said characteristic is said indications of brain inflammatory reactions.

¹⁷²
Claim ~~280~~ (Currently Amended) The method of claim ~~279~~ ¹⁷¹, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of

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chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹⁷³
Claim ~~281~~ (Currently Amended) The method of claim ~~280~~¹⁷², wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹⁷⁴
Claim ~~282~~ (Previously Added) The method of claim ~~279~~¹⁷¹, where said brain cells are in the form of dissociated cells.

¹⁷⁵
Claim ~~283~~ (Previously Added): The method of claim ~~279~~¹⁷¹, wherein said brain cells are in the form of a brain slice.

¹⁷⁶
Claim ~~284~~ (Currently Amended) The method of claim ~~283~~¹⁷⁵, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, or and a cortex slice.

Claim 285 (Cancelled)

¹⁷⁷
Claim ~~286~~ (Currently Amended) The method of any one of claims ~~279-285~~¹⁷¹⁻¹⁷⁶ ~~279-284~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹⁷⁸
Claim ~~287~~ (Previously Added) The method of claim ~~286~~¹⁷⁷, wherein said rodent is a mouse.

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¹⁷⁹
Claim ~~288~~ (Previously Added) The method of claim ~~286~~¹⁷⁷, wherein said rodent is a rat.

¹⁸⁰
Claim ~~289~~ (Currently Amended) The method of any one of claims 279-285 ~~279-284~~¹⁷¹⁻¹⁷⁶, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

¹⁸¹
Claim ~~290~~ (Previously Added) The method of claim ~~289~~¹⁸⁰, wherein said rodent is a mouse.

¹⁸²
Claim ~~291~~ (Previously Added) The method of claim ~~289~~¹⁸⁰, wherein said rodent is a rat.

¹⁸³
Claim ~~292~~ (Previously Added) The method of claim ~~213~~¹¹⁰, wherein said characteristic is said conversion of p35 to p25.

¹⁸⁴
Claim ~~293~~ (Currently Amended) The method of claim ~~292~~¹⁸³, wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹⁸⁵
Claim ~~294~~ (Currently Amended) The method of claim ~~293~~¹⁸⁴, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

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¹⁸⁶
Claim ~~295~~ (Previously Added) The method of claim ~~292~~¹⁸³, where said brain cells are in the form of dissociated cells.

¹⁸⁷
Claim ~~296~~ (Previously Added): The method of claim ~~294~~¹⁸⁵, wherein said brain cells are in the form of a brain slice.

¹⁸⁸
Claim ~~297~~ (Currently Amended) The method of claim ~~296~~¹⁸⁷, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 298 (Cancelled)

¹⁸⁹
Claim ~~299~~ (Currently Amended) The method of any one of claims 292-298 ~~292-297~~¹⁸³⁻¹⁸⁸, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

¹⁹⁰
Claim ~~300~~ (Previously Added) The method of claim ~~299~~¹⁸⁹, wherein said rodent is a mouse.

¹⁹¹
Claim ~~301~~ (Previously Added) The method of claim ~~299~~¹⁸⁹, wherein said rodent is a rat.

¹⁹²
Claim ~~302~~ (Currently Amended) The method of any one of claims 292-298 ~~292-297~~¹⁸³⁻¹⁸⁸, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

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¹⁹³
Claim ~~303~~ (Previously Added) The method of claim ~~302~~¹⁹², wherein said rodent is a mouse.

¹⁹⁴
Claim ~~304~~ (Previously Added) The method of claim ~~302~~¹⁹², wherein said rodent is a rat.

¹⁹⁵
Claim ~~305~~ (Previously Added) The method of claim ~~213~~¹¹⁰, wherein said characteristic is said changes in the level and/or activity of cyclin dependent protein kinase 5 (cdc5).

¹⁹⁶
Claim ~~306~~ (Currently Amended) The method of claim ~~305~~¹⁹⁵, wherein said compound is selected from the group consisting of a compound which is selected from the group consisting of chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

¹⁹⁷
Claim ~~307~~ (Currently Amended) The method of claim ~~306~~¹⁹⁶, wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

¹⁹⁸
Claim ~~308~~ (Previously Added) The method of claim ~~305~~¹⁹⁵, where said brain cells are in the form of dissociated cells.

¹⁹⁹
Claim ~~309~~ (Previously Added): The method of claim ~~305~~¹⁹⁵, wherein said brain cells are in the form of a brain slice.

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²⁰⁰
Claim ~~310~~ (Currently Amended) The method of claim ~~309~~¹⁹⁹, wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 311 (Cancelled)

²⁰¹
Claim ~~312~~ (Currently Amended) The method of any one of claims ~~305-311~~¹⁹⁵⁻²⁰⁰ ~~305-310~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

²⁰²
Claim ~~313~~ (Previously Added) The method of claim ~~312~~²⁰¹, wherein said rodent is a mouse.

²⁰³
Claim ~~314~~ (Previously Added) The method of claim ~~312~~²⁰¹, wherein said rodent is a rat.

²⁰⁴
Claim ~~315~~ (Currently Amended) The method of any one of claims ~~305-311~~¹⁹⁵⁻²⁰⁰ ~~305-310~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

²⁰⁵
Claim ~~316~~ (Previously Added) The method of claim ~~315~~²⁰⁴, wherein said rodent is a mouse.

²⁰⁶
Claim ~~317~~ (Previously Added) The method of claim ~~315~~²⁰⁴, wherein said rodent is a rat.

²⁰⁷
Claim ~~318~~ (Previously Added) The method of claim ~~315~~¹¹⁰, wherein said characteristic is said changes in the level and/or activity of mitogen activated protein kinases.

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²¹³
Claim ~~325~~ (Currently Amended) The method of any one of claims ~~318-324~~ ²⁰⁷⁻²¹² ~~318-323~~, wherein said rodent brain cells are apolipoprotein E-deficient rodent brain cells.

²¹⁴
Claim ~~326~~ (Previously Added) The method of claim ~~325~~ ²¹³, wherein said rodent is a mouse.

²¹⁵
Claim ~~327~~ (Previously Added) The method of claim ~~325~~ ²¹³, wherein said rodent is a rat.

²¹⁶
Claim ~~328~~ (Currently Amended) The method of any one of claims ~~318-324~~ ²⁰⁷⁻²¹² ~~318-323~~, wherein said rodent brain cells are apolipoprotein E-containing rodent brain cells.

²¹⁷
Claim ~~329~~ (Previously Added) The method of claim ~~328~~ ²¹⁶, wherein said rodent is a mouse.

²¹⁸
Claim ~~330~~ (Previously Added) The method of claim ~~328~~ ²¹⁶, wherein said rodent is a rat.

7. Authorization for this examiner's amendment was given in a telephone interview with Michele Cimbala (Reg. No. 33851) on 7 October 2003.

Summary

8. Claims 95-101, 103-114, 116-127, 129-140, 142-153, 155-166, 168-179, 181-192, 194-205, 207-219, 221-232, 234-245, 247-258, 260-271, 273-284, 286-297, 299-310, 312-323, and 325-330 are hereby allowed.

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²⁰⁸
Claim ~~319~~ (Currently Amended) The method of claim ~~318~~,²⁰⁷ wherein said compound is selected from the group consisting of ~~a compound which is selected from the group consisting of~~ chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and beta-amyloid.

²⁰⁹
Claim ~~320~~ (Currently Amended) The method of claim ~~319~~,²⁰⁸ wherein said compound is N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone ZPAD.

²¹⁰
Claim ~~321~~ (Previously Added) The method of claim ~~318~~,²⁰⁷ where said brain cells are in the form of dissociated cells.

²¹¹
Claim ~~322~~ (Previously Added): The method of claim ~~318~~,²⁰⁷ wherein said brain cells are in the form of a brain slice.

²¹²
Claim ~~323~~ (Currently Amended) The method of claim ~~322~~,²¹¹ wherein said brain slice is selected from the group consisting of a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, ~~or~~ and a cortex slice.

Claim 324 (Cancelled)

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9. The Examiner acknowledges that acceptance of the above Examiner's Amendment does not mitigate in any way, shape, or form, Applicant's right to pursue additional subject matter in continuation, continuation-in-part, and/or divisional applications pursuant to 35 U.S.C. §120 and §121.

10. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon for the grounds of a rejection, are here made of note:

- a. US 5849691 (15 December 1998) Majer *et al.*
- b. US 5686269 (11 November 1997) Nixon
- c. US 5747517 (5 May 1998) Panetta *et al.*
- d. US 6251928 (26 June 2001) Panetta *et al.*
- e. US 5858982 (12 January 1999) Tung *et al.*
- f. US 2002/0094958 A1 (18 July 2002) Bahr
- g. Goldsby *et al.* KUBY Immunology 4th Ed. (pp. 617)

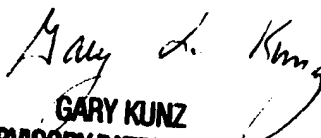
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
October 7, 2003


GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600